IIV Working Group: National Children's Study

Proposed Core Hypothesis:

The receipt of childhood routine vaccination is not linked to Autism or other developmental disabilities identified during childhood and adolescence

Draft

Submitted to Dr. Robert Yolken and Dr. Bill Rodriguez

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NOTE: This draft core hypothesis was proposed on behalf of the infectious disease/vaccine group, and is not indicative of a commitment from NIAID to sponsor such research.

I. Proposed core hypothesis question

The National Children's Study (NCS) plans to collect data for a large cohort of infants followed into young adulthood. To be adequately tested, the proposed hypothesis requires the full length and breadth of this prospective study, including active ascertainment of vaccine adverse events.

This proposed core hypothesis for the vaccine/infectious disease section:

The receipt of childhood routine vaccination is not linked to Autism or other developmental disabilities identified during childhood and adolescence. Also, and linked to these concerns, childhood vaccination is not linked to inflammatory bowel disease (IBD), including Crohn's disease.

The hypothesis is stated in the negative, as we do not believe this to be the case. For example, most studies agree that the purpoted association between receipt of MMR vaccine and the onset of autism in infancy/childhood is most likely coincidental. However, because of high publicity of a handful of studies suggesting such links between MMR and autism and IBD, this possibility remain a major reason for parents opting to avoid MMR vaccination for their infants, there is a critical need for a definitive study to settle this question.

Examples of specific research questions hosted within this core hypothesis are:

- **Is the receipt of MMR doses (1 or 2) linked to Autism or any other severe psychogenic diagnoses ?**
- **Is there a relationship between Autism/developmental disabilities, IBD and receipt of childhood vaccines?**
- **Is there a relationship between DPT vaccination and encephalopathy or serious neurologic illness or SIDS?**
- **Is the receipt of any childhood vaccine (other than MMR) linked to any developmental disabilities?**
- **In the case of onset of developmental disabilities associated with receipt of later vaccine doses (for example DTP dose 3,4 or MMR2) – was there an overrepresentation of milder adverse events/symptoms associated with the first dose(s) of that vaccine or a family history?**
- **For infants with autism or other disorders of cognitive function that may be of concern as possible vaccine related events – what is the role of overexpression of neuropeptides and neurotrophins? Are there risk factors such as particular HLA types, etc?**

This large cohort study of ~100,000 infants will capture key data needed regarding to vaccines received, timing of each dose, age at each dose, vaccine-related adverse events

for each vaccination event, as well as all information regarding ill visits, hospitalizations and any diagnoses given during infancy and childhood. With additional basic genetic data on each child, and possibly their parents and siblings, this cohort study database may allow for studies of genetic determinants for severe adverse vaccine reactions. Further, the systematically collected survey data from mothers regarding vaccine adverse events, and data collected on family history of such outcomes among parents and siblings, will allow for an unique opportunity to study the linkage of vaccination events and the onset of key symptoms of rare possibly vaccine related outcomes. Indeed, if a large proportion of severe vaccine adverse events occur among a subset of children with genetic predispositions, it might be possible to sharply reduce such outcomes on routine vaccinations. Such genetic and statistical tools are needed to address this hypothesis, because the frequency of autism in the population is relatively low (~100 in 100,000 population).

II. Workgroup collaboration

I welcome and encourage collaboration with NCS groups, as well as agencies and groups outside of the NCS, in the US or abroad, concerned with issues of vaccine safety.

III. Contact person for proposed core hypothesis question

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IV. Public health significance

The core hypothesis aims to determine if an association exists between the receipt of infant vaccine doses and developmental disorders such as autism. In recent years, the purpoted association between MMR vaccination and autism in childhood has unfortunately led to a marked increase in parents who prefer to avoid this vaccine for their infants. Such mistrust in childhood vaccine safety also has tended to generate a general mistrust in the infant vaccine schedule, and groups of parents connected via internet etc .

Identification of vaccine adverse events occurs both before and after licensure. Epidemiologically, a cause-and-effect association is greatly strengthened by a

determination that the rate of a given illness following immunization is significantly higher than the rate of that illness in the absence of vaccination. The possibility that a subset of the infant cohort have genetic predisposition to vaccine-adverse events remains to be thoroughly explored. For example, a recent study found that over-expression of certain neuropeptides and neurotrophins (such as vasoactive intestinal peptide VIP) observed in blood samples drawn in the first days of life were strongly predictive of autism and other disorders of cognitive function diagnosed later in childhood [Nelson 2001]. Overall, there has been little exploration of major biological regulators of cerebral development in autism.

Autism:
The CDC estimates the prevalence of autism to be ~100 per 100,000 population in the U.S, while as many as 200-500 per 100,000 children may exhibit some form of developmental disabilities including physical, cognitive, psychological, sensory and speech impairments that are usually identified between birth and up to age 18 years. It is estimated that about 17% of all children have a developmental disability such as mental retardation, cerebral palsy or autism. Autism occurs in all racial, ethnic and social groups, but 3-4 times more often among boys than girls. The diagnosis is usually confirmed around the age of 2 when the child fails to develop functional language. Approximately 20% of children with autism experience "regression", e.g., a loss of communiation/social skills after normal development [CDC/NIP website]. Autistic "regression" has been associated with MMR vaccination, and a new syndrome proposed of MMR-induced IBD/autism [Wakefield, 1993]. Numerous other studies have documented no change in autism prevalence before and after introduction of MMR, or that increases in autism prevalence occurred while there was no change in MMR vaccination coverage [CDC/NIP website].

Inflammatory Bowel Disease (IBD): Two common inflammatory bowel diseases are ulcerative colitis and Crohn's disease. IBD are known to "run in families", suggesting a possible inherited or genetic cause. Although IBD can begin at any age, it's usual onset is from 15 to 30 years of age. IBD is a rare disease with 3-20 new cases recognized per 100,000 persons per year. At ~10 new cases identified per year during the age of 15-20, I estimate that the prevalence of IBD in this cohort study may be on the order of ~50 per 100,000 persons. MMR vaccine (as well as natural measles infection) has been suggested as a possible cause of IBD (Wakefield 1998) and Crohn's disease (Ekbom 1994; 1996; and Thompson 1995).

V. Justification for a large, prospective, longitudinal study

A sufficiently large cohort, widely diverse, with consistent, reliable long-term follow-up for serious health outcomes at least into adolescence would offer a great opportunity to explore multiple vaccine safety related questions.

The annual US birth cohort exposed to universal vaccination is approximately 4 million infants. With advancements from older vaccine types to newer (e.g., live attenuated or inactivated poliovirus vaccine), alterations in adjuvants (e.g., thimerasol), and other innovations, new vaccines can be recommended for universal use in that annual birth cohort. The vaccine adverse effects often cannot be sufficiently addressed when they are rare (<1:1000) short-term adverse events, longer-term adverse events, or in diverse subsets of infants not previously evaluated.

The introduction of combination vaccines and of multiple concurrent immunizations further complicates evaluation and separation of individual vaccine effects. Vaccine manufacturers and public health agencies are well aware of these limitations, and are working to address these critical safety questions. There are feasibility, economic and risk:benefit considerations that make much larger comparative clinical trials prior to vaccine licensure and universal use highly unlikely for every new vaccine. Even existing post-marketing safety evaluation systems, such as the CDC Vaccine Datalink, lack the ability to follow children for many years.

Thus, recommendations for immunization practices balance scientific evidence of benefits for each person and to society against the potential costs and risks of vaccination programs." [MMWR CDC Surveillance Summary 2002 Feb 8; 51 (RR-2): 1-35] Yet the safety questions persist. The scope and duration of the National Children's Study will permit numerous vaccine safety questions to be addressed.

VI. Scientific merit

The available comparative information at the time of vaccine licensure and introduction to the general population is limited by the duration of vaccine development, such that the only adverse events observed occur within a few years of vaccination. Further, this pre-licensure information is probably non-existent for rare outcomes such as autism.

The questions proposed for childhood vaccination are one of many vaccine safety related questions to be addressed under this core hypothesis. If we can successfully rule out childhood vaccines as a cause of severe adverse events, surely this will be an important rationale for parents to ensure adherence to the recommended schedule.

The Institute of Medicine, in its recently issued Immunization Safety Review (2001) and in several vaccine safety workshops, has called for the evaluation of longer term outcomes. "According to workshop participants, these findings reinforce the need for long term studies to determine late-onset adverse effects of vaccines." [Vaccine Safety Forum: Summary of Two Workshops (1997)] A cohort of 100,000 represents 2.5% of the annual birth cohort, and follow-up of decades represented approximately ten times the usual duration of post-vaccination follow-up. The National Children's Study affords an invaluable opportunity to evaluate vaccine safety in a much more heterogeneous cohort, and for observation of longer term outcomes than has previously been available.

VII. Potential for innovative research

The National Children's Study provides the potential to incorporate or react to new vaccine developments that may occur during the exposure period of those children enrolled, such as edible vaccines (e.g., bananas or tomatoes). Depending upon the timing and geographic introduction of such new vaccines, those receiving and not receiving the new vaccines could be compared and contrasted. Genetic analyses may provide links, as yet unknown, that identify individuals predisposed to severe vaccine-adverse events. The range of potential pioneering research that might impact the cohort enrolled could be limitless.

VIII. Feasibility

Critical period for exposure and outcomes – The critical period for exposure to childhood immunizations is defined as the period between birth and three years of age, when receipt of recommended immunizations should be complete.

Sampling needs – The CDC estimates the prevalence of autism to be ~100 per 100,000 population in the U.S, while as many as 200-500 per 100,000 children may exhibit some form of the disorder [CDC/NIP website]. Other development disabilities including physical, cognitive, psychological, sensory and speech impairments are more prevalent.

Testing of the proposed hypotheses would thus require the full cohort of NCS participants. With the possibility of over-sampling of special population subgroups (e.g., Hispanics, Native Americans), some of the proposed hypotheses may for the first time be addressed in minority populations.

Number, frequency and timing of study contacts – Initial contact will occur at first enrollment and at the time of the first vaccination. Subsequent contacts will occur after age 3 to collect vaccination histories and other information, and at approximately 5-year intervals thereafter (at the minimum) to test for autism symptoms and update medical history and other information.

Community involvement – Requires cooperation of parents, teachers, and local health professionals, although this is not expected to pose additional burden beyond the scope of what already is proposed for the NCS.

Other burden to the participant and family associated with this hypothesis -- None expected. If autism disease is identified, referral information may be provided for follow-up treatment.